Journal of Surgical Oncology 1997;65:88–94

Complications of Combined Radiotherapy and Isolated Limb Perfusion With Tumor Necrosis Factor Alpha ± Interferon Gamma and Melphalan in Patients With Irresectable Soft Tissue Tumors

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Background: Isolated limb perfusion (ILP) with tumor necrosis factor alpha (TNFα) ± interferon gamma (IFNγ) and melphalan in patients with primarily irresectable soft tissue sarcoma is promising in terms of tumor regression and limb salvage. However, the feasibility of radiotherapy in combination with this treatment modality has not been established.

Methods: Fifteen patients with irresectable soft tissue tumors of the limb underwent ILP with TNFα, ±IFNγ, and melphalan. Three groups could be distinguished with respect to the role of radiotherapy. In nine patients, the residual tumor could be resected after ILP, and this was followed by radiotherapy with a total dose of 50–70 Gy (2 Gy/day). In one patient with aggressive fibromatosis, ILP was followed by radiotherapy without tumor resection (Group I). In two patients who underwent ILP for recurrent sarcoma, the primary tumor had been treated before by resection and radiotherapy (60 Gy) (Group II). In three patients whose tumors remained irresectable after ILP, radiotherapy was applied later in the course of disease for local palliation (Group III).

Results: In Group I, healing of the resection wound was markedly delayed in four patients, with soft tissue necrosis and infection necessitating amputation in two of them. Following completion of radiotherapy, persistent lymphoceles were encountered in two patients. Radiotherapy-induced fibrosis was encountered in five patients, resulting in a mild limb malfunction in two. Three patients developed mild edema during radiotherapy. Tumor-associated neuropathy was aggravated by ILP in three patients causing severely disabling motor deficits and limb contractures in two of them. In Group II, ILP did not cause any local problem in the heavily irradiated areas. In Group III, pre-existing limb edema was increased after a total palliative dose of 20 Gy in one patient. Another patient, who had been re-operated for arterial thrombosis immediately after ILP, developed occlusion of the brachial artery 4 months after completion of palliative radiotherapy (36 Gy in 6 Gy fractions).

Conclusions: In patients with irresectable soft tissue tumors, multimodal-

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Accepted 10 February 1997

ity treatment using ILP with TNFα ± IFNγ and melphalan, tumor resection, and postoperative high-dose radiotherapy is associated with a considerable risk of tissue necrosis and impaired healing. This risk should be weighed against a possible benefit from radiotherapy in local tumor control. *J. Surg. Oncol. 1997;65:88–94.*

KEY WORDS: sarcoma; morbidity; wound healing; lymphocele

INTRODUCTION

For most soft tissue sarcomas of the limb, locoregional control can be achieved by conservative surgery combined with radiotherapy [1]. However, for locally advanced, irresectable tumors, it is still difficult to obtain satisfactory local disease control without amputation or severe functional morbidity. In these cases, isolated limb perfusion (ILP) appears to be appropriate. Preoperative ILP can reduce the size of the tumor and render it operable [2–5]. In some cases of limb sarcoma with systemic metastases, ILP can be used in a palliative sense for the alleviation of local symptoms while avoiding ablative or mutilating surgery [2,4]. Earlier studies of ILP (with various cytostatic agents) have shown meager response rates and considerable regional toxicity [4,6–8].

However, preliminary results with ILP using the recently introduced biological response modifier tumor necrosis factor alpha (TNFα) are promising. Liénard et al. [9] obtained complete responses in four patients with advanced limb sarcomas, applying high-dose TNFα in combination with melphalan and interferon gamma (IFNγ), without severe limb toxicity. Results from a recent international multicenter study in 54 patients with irresectable soft tissue tumors showed a complete response rate of 38% and a partial response rate of 52% after ILP with TNFα, IFNγ, and melphalan, rendering the tumor operable in a substantial number of partial responders [10,11].

At this time, it is not clear what the best additional treatment is after a partial response has been obtained. The optimal margin for local excision has not been established but will often, perforce, be narrow in these patients. Frequently, further treatment has to be considered when vital tumor tissue is found in the excision margins. The role and feasibility of postoperative radiotherapy are still unknown since massive tumor necrosis and ulceration of overlying skin combined with impaired wound healing have been reported after ILP using TNFα [11,12]. Furthermore, radiotherapy has been related to the development of wound complications, soft tissue necrosis, and fibrosis [13].

Recently, we have treated a number of patients with soft tissue tumors by both radiotherapy and ILP using TNFα and melphalan. In a literature search using MEDLINE, no reports on the feasibility of such a treatment combination could be found. The purpose of this retrospective study was to assess nature and incidence of complications with this combined treatment.

MATERIALS AND METHODS

From October 1992 to December 1994, 22 patients with irresectable soft tissue tumors of the limbs underwent ILP with TNFα ± IFNγ and melphalan in The Netherlands Cancer Institute. Treatment results are reported elsewhere since these ILPs were carried out as part of an international multicenter study [14]. The 15 patients who have been submitted to radiotherapy of the perfused limb during some phase of treatment were selected for this study.

Patient and tumor characteristics are summarized in Table I. Included were 10 male and five female patients with a median age of 49 years (mean age 51 years; range 30–71 years). The upper limb was involved in five and the lower limb in 10 patients. The selection criteria for ILP are shown in Table II. All patients were perfused because of a non-resectable tumor. Two patients had recurrent disease at the original tumor site. The mean tumor size was 15 cm (range 6–30 cm). One patient was perfused twice in an idle attempt to render the process operable. In another patient with systemic metastases, the local tumor growth threatening the limb required palliative ILP in order to avert amputation. Eight different types of soft tissue tumor were involved (Table I). The histologic grading of the tumors was based on mitosis counts [15,16].

Treatment data are summarized in Table III. Our perfusion methodology has been described previously in detail [17,18]. The TNFα ILP protocol included a high dose of TNFα: 4 mg for the iliac and femoral, and 3 mg for the axillary and brachial ILPs. In four patients, 0.2 mg IFNγ was injected subcutaneously for 2 days before surgery. The same dose was given during the ILP. In the remaining 11 patients, IFNγ was omitted as they were entered in a multicenter trial evaluating the role of this cytokine [14,19]. TNFα ± IFNγ was injected as a bolus into the arterial line of the perfusion circuit. Melphalan was administered 30 minutes later in the routine dose of 13 mg per liter perfused tissue for upper limb and 10 mg per liter perfused tissue for lower limb procedures. Patients were subjected to a tissue temperature level of 38–40°C, so-called mild hyperthermia. Seven ILPs were performed

TABLE I. Patient and Tumor Characteristics of 15 Patients With Irresectable Soft Tissue Tumors Treated by Combined Radiotherapy and Isolated Limb Perfusion With Tumor Necrosis Factor Alpha With or Without Interferon Gamma and Melphalan

	Sex	Age (yr)	Limb	Tumor type	Size (cm)	Grade	Indication for ILP
Group I							
1	M	69	leg	liposarcoma	20	G1	1
2	F	43	leg	malignant schwannoma	14	G1	1
3	M	60	leg	unclassified	12	G1	1
4	M	32	leg	MFH[a]	9	G2	1
5	M	71	arm	unclassified	8	G2	1
6	F	57	leg	liposarcoma	20	G1	1
7	M	35	leg	liposarcoma	30	G1	1
8	M	55	leg	MFH[a]	15	G1	1
9	M	37	arm	aggressive fibromatosis	14	G1	1
10	F	69	leg	liposarcoma	12	G1	1
Group II							
11	M	68	arm	liposarcoma	12	G2	2
12	F	40	leg	liposarcoma	15	G3	2
Group III							
13	F	66	arm	synoviosarcoma	11	G2	3
14	M	31	arm	Merkel cell carcinoma	6	—	1
15	M	30	leg	epitheloid sarcoma	23	G3	1

[a]Malignant fibrous histiocytoma.

TABLE II. Indications for Isolated Limb Perfusion (ILP)

1	Irresectable soft tissue sarcoma grade 2 or 3 (any size) or grade 1 (>8 cm) that necessitates amputation or can be resected only at the cost of unacceptable functional morbidity
2	Local recurrence (grade 1 > 8 cm, grade 2 or 3) if treated before by surgery and/or radiotherapy or by ILP with chemotherapy alone
3	Metastatic disease at the time of presentation of a primary tumor that can be resected only by amputation or unacceptable functional morbidity

at the iliac, three at the femoropopliteal, one at the axillary, and four at the brachial isolation level. Acute regional toxicity was graded according to Wieberdink et al. [20].

No complete remissions were seen after ILP in these 15 patients. Residual tumors were resected after maximal shrinkage. In nine patients, resection of the residual tumor could be performed after a median period of four months (mean period 4 months; range 2.5–5.5 months) after ILP. In one patient the resection margins were macroscopically involved with tumor. In the remaining eight patients, the resection margins were macroscopically tumor-free but on microscopic examination involved in five and only marginally tumor-free in three patients. In the remaining six patients, the tumor was not rendered operable by ILP. These latter patients were subjected to radiotherapy with curative intent (one patient with aggressive fibromatosis), palliative radiotherapy (three patients, all with hematogenic dissemination), amputation (one patient), and no further treatment (one patient with hematogenic spread).

Three groups could be distinguished according to the role of radiotherapy. Group I included 10 patients who received high-dose radiotherapy with curative intent following ILP. In nine of these patients the residual tumor had been irradically or marginally resected, one patient with aggressive fibromatosis received radiotherapy without additional surgery. Group II included two patients who were perfused for recurrent disease and whose primary sarcomas had previously been treated by resection and high-dose radiotherapy. Group III included three patients who received palliative radiotherapy for locoregionally intractable disease following ILP ± resection.

In group I, the guidelines for radiotherapy for primary sarcoma with large fields were generally followed [21]. High-dose external beam radiotherapy consisted of an initial dose of 50 Gy (5 fractions of 2 Gy per week) on the tumor bed followed by a boost of 10–20 Gy on areas with suspected residual tumor. The final dose depended also on the wound healing and the condition of the limb at the time of treatment. For the patient with aggressive fibromatosis, a total dose of 50 Gy was considered to be adequate. Radiotherapy was planned to start within 6 weeks after surgery. If wound healing was not complete by that time the radiotherapy was delayed until (near) complete healing occurred. In this group of patients, the median interval between surgery and the start of radiotherapy was 6 weeks (range 4–12 weeks). The median follow-up time after completion of radiotherapy was 8 months (range 4–17 months). The two patients in group II had undergone resection of their primary tumors followed by radiotherapy with a total dose of 60 Gy (2

TABLE III. Treatment Characteristics of 15 Patients With Irresectable Soft Tissue Tumors Treated by Combined Radiotherapy and Isolated Limb Perfusion (ILP) With Tumor Necrosis Factor Alpha With or Without Interferon Gamma (IFNγ) and Melphalan

Group I

	ILP IFN-γ	Level	Wieberdink grade[a]	Excision	Radiotherapy indication[b]	Total dose
1	no	iliac	II	yes	NM	50 Gy
2	no	iliac	II	yes	MiRD	60 Gy
3	yes	iliac	III	yes	NM	50 Gy
4	yes	femoral	IV	yes	NM	60 Gy
5	no	brachial	III	yes	MiRD	53 Gy
6	no	popliteal	II	yes	MaRD	56 Gy[c]
7	no	iliac	II	yes	MiRD	70 Gy
8	no	iliac	II	yes	MiRD	66 Gy
9	no	brachial	II	no	—	50 Gy
10	no	femoral	II	yes	MiRD	60 Gy

Group II

	Radiotherapy Total dose	Boost	ILP IFNγ	Level	Wieberdink grade	Excision
1	60 Gy	no	no	brachial	II	no
2	60 Gy	no	no	iliac	II	amputation

Group III

	ILP IFNγ	Level	Wieberdink grade	Resection	Radiotherapy Scheme
1	no	brachial	II	no	6 × 6 Gy
2	yes	axillary	III	yes	10 × 3 Gy (on 3 sites)
3	yes	iliac	II		
	yes	iliac	II	no	5 × 4 Gy (on 2 sites)

[a]I, no reaction; II, slight erythema and/or edema; III, considerable erythema, edema and blistering; IV, compartmental compression syndrome; V, reaction necessitating amputation.
[b]NM: complete resection with narrow margins (<1 cm); MiRD: microscopic residual disease; MaRD: macroscopic residual disease.
[c]Radiotherapy was stopped prematurally because of wound complications.

Gy/day) 15 and 116 months before ILP, respectively. Follow-up times after ILP were 16 and 14 months, respectively. The three patients in group III were treated with various radiotherapy schedules for palliative reasons. Intervals between ILP and start of palliative radiotherapy were 6, 8, and 16 months, respectively, and the duration of follow-up was 11, 7, and 10 months.

RESULTS

Group I

Complications are summarized in Table IV. The early radiation-induced skin reactions (erythema, dry desquamation) were comparable to those usually seen after doses of 50–60 Gy.

In one of the 10 patients no morbidity was encountered at 4 months after completion of radiotherapy. Amputation had to be performed in two patients (20%), because of nonhealing of the resection wounds and the occurrence of ulcerating skin defects with subsequent tissue necrosis and infection during radiotherapy.

In two of the remaining seven patients, the excision wounds showed no tendency of healing at 4 and 8 months after completion of radiotherapy. One of them also suffered from a persistent lymphocele and recurrent erysipelas of the treated limb. In another patient, lymphocele formation continued for 6 months following completion of radiotherapy. Marked fibrosis was encountered in five of the seven patients, in three cases accompanied by mild edema. In one of these patients, fibrosis occurred after ILP and was already present at the start of radiotherapy. Only two patients had a single complication. The complications observed did not occur more frequently in patients receiving the highest radiation dose.

Limb malfunction was encountered in four of the eight patients without amputation: in two cases this was mild (due to fibrosis) and in two severely disabling (due to peroneal nerve motor deficits). In the latter two patients, neuropathy was pre-existing, caused by the tumor and preceding surgery, but was severely aggravated after ILP.

Group II

One of the previously irradiated patients had no complications after ILP. The other patient developed a tem-

TABLE IV. Complications of Radiotherapy Combined With Isolated Limb Perfusion (ILP) With Tumor Necrosis Factor Alpha With or Without Interferon Gamma and Melphalan With or Without Tumor Resection

	Number of patients
Group I (n = 10)	
No complications	1
Amputation	2
Wound healing problems	2
Persistent lymphocele	2
Fibrosis	5
Edema	3
Neuropathy[a]	2
Limb malfunction	
mild disabling	2
severe disabling	2
Group II (n = 2)	
No complications	1
Neuropathy (temporary)	1
Group III (n = 3)	
No complications	1
Edema	1
Arterial occlusion	1

[a]Due to tumor growth and aggravated by ILP.

porary peroneal nerve palsy in the first 24 hours after ILP.

Group III

One of the three patients who underwent palliative radiotherapy was spared from posttreatment complications. A second patient was re-operated after ILP for acute brachial artery occlusion and developed recurring brachial artery occlusion four months after radiotherapy. In the third patient, pre-existing edema worsened after radiotherapy.

DISCUSSION

During the last two decades, limb salvage has gradually replaced amputation as the treatment of choice for locally advanced soft tissue sarcomas of the extremities [1]. In addition to alleviating the local problem and curing the patient, a third goal is to preserve function and cosmesis as much as possible [22]. Adequate local resection, however, demands taking a substantial rim of uninvolved tissue around the tumor in order to prevent local recurrence [23,24]. Frequently, this requirement cannot be met due to tumor size and/or the vicinity of vital structures. Surgery combined with radiotherapy in these cases can decrease the risk of local recurrence to ~10–20% [1,21,25–27]. ILP is an alternative in advanced sarcomas that require amputation of the limb or can only be resected at the cost of unacceptable functional morbidity [2–5,22,28]. Extensive excision or even amputation in these cases is obviously difficult to accept especially in view of the frequent appearance of distant metastases within a short interval after the ablative treatment.

Preliminary results of ILP using TNFα and melphalan (with or without IFNγ) have been encouraging, with limb salvage in almost 90% of the patients [14]. However, as the majority of these patients show only partial tumor regression after ILP, further radical surgery, eventually followed by postoperative radiotherapy, remains the cornerstone in local tumor control.

Our experience showed that the intensive treatment protocol of ILP with TNFα, resection, and high-dose radiotherapy is accompanied by major complications, especially in the form of wound healing problems and tissue necrosis (44%). In two patients, the affected limb had to be amputated for these reasons. One could argue that amputation was indicated anyway in these patients, but the costs in quality of life during the complicated treatment period and the delay in definitive surgery of ~1 year do not justify this view.

Wound healing problems following ILP using TNFα have been reported in another series as well [12]. In that study this complication was associated with massive tumor necrosis and loss of uninvolved skin overlying the tumor [12]. Wound problems also occur after combination therapy using local surgery and radiotherapy for advanced limb sarcomas [13,25,29] and even in sarcoma patients treated by surgery alone, wound complication rates as high as 28–33% have been reported [30].

Tissue necrosis and wound complications also have been observed in sarcoma patients after ILP using other cytostatic drugs [28,31]. In a series of 13 patients with locally advanced osteogenic sarcoma, four limbs (31%) had to be amputated because of infection and lack of healing, 6–12 months after hyperthermic (41–41.5°C) ILP using cisplatin combined with tumor resection and radiotherapy (36 Gy) [28]. Because of these serious problems, the authors decided to drop radiotherapy from the treatment protocol [28]. In another study applying ILP with melphalan and actinomycin D followed by resection of the sarcoma, wound healing problems did not allow a complete course of radiotherapy (50 Gy) [31]. However, Rossi et al. [32] did not observe any delayed wound healing in 11 patients with limb sarcoma treated by hyperthermic ILP (40.5–42°C) using doxorubicin, marginal resection, and postoperative radiotherapy (54 Gy in 27 fractions).

The approach of starting postoperative radiotherapy only after complete healing of the resection wound has the disadvantage that residual tumor cells are allowed to proliferate in the often protracted interval between resection and radiotherapy [1].

Early radiation-induced reactions have been reported to be mild and do not seem to be influenced by the preceding ILP [33]. Fibrosis, a commonly reported late side-effect after high-dose radiotherapy, was encountered

in most patients. Functional disturbances could be limited by intensive physiotherapeutic support in all but two patients in whom joint function was mildly affected.

The complications observed did not occur more frequently in patients receiving the highest radiation dose. However, the small number of patients does not permit any conclusion on a possible correlation between the radiation dose and the complication rate.

In two patients, pre-existing neuropathy was markedly aggravated after ILP, probably as a result of necrosis and edema of the tumor in the direct postoperative period.

ILP using TNFα in irradiated limbs did not result in local complications in our series. Blistering and necrosis developing in a previously irradiated area, however, have been reported after ILP and seem compatible with reports by other authors on the reciprocally potentiated effects of cytostatic drugs and radiotherapy [4,34,35].

Palliative radiotherapy did not lead to major problems in the perfused limb, apart from vascular complications following a 6 × 6 Gy schedule, which could, however, also have been a result from an arterial thrombosis following ILP.

CONCLUSIONS

Multimodality treatment using ILP with TNFα ± IFNγ and melphalan, combined with tumor resection and high-dose radiotherapy, is associated with a considerable risk of tissue necrosis and impaired wound healing. In view of the only alternative for ILP in these patients, i.e., amputation, we are of the opinion that these complications are still acceptable. The need for postoperative radiotherapy in these patients should be established in future studies focussing on local tumor control. Although the number of cases reported is limited, ILP using TNFα in a previously irradiated limb and conventional palliative radiotherapy after TNFα-ILP do not seem to impose an increased risk of local complications.

ACKNOWLEDGMENTS

We thank G.W. van Slooten, perfusion technician, and the laboratory technicians of the Department of Nuclear Medicine for their indispensable assistance.

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